#15: Most studies use PTOA to test the efficacy of a DMOAD. Should this also be tested in an aging model?

Yuwei Zhang, Xiangkai, Meagan Makarczyk, Olivia Bartholomew, Tomoya Iseki, Benjamin Rothrauff, Ning Wang, Zhong Alan Li, Hang Lin

Response/Recommendation: Yes. Some treatments show different efficacies across the two models, and animal species might contribute to this inconsistency. Thus, simultaneously testing DMOADs in trauma-induced and aging-associated OA models in the same animal species, male and female, is necessary before clinical trials to maximize the prediction power of preclinical models.

Level Of Evidence: Moderate

Rationale:

Osteoarthritis (OA) is well known as an aging-associated disease, and the majority of OA patients are older adults (typically over the age of 60) [1]. Therefore, the model for testing disease-modifying osteoarthritis drugs (DMOADs) should use aged animals. However, working with older animals can be both cost- and time-prohibitive. As a result, posttraumatic osteoarthritis (PTOA) in young animals currently dominates the landscape of preclinical DMOAD development. While these PTOA models induce rapid, reproducible structural changes, comparative studies have shown that the molecular and structural differences between PTOA and aging-associated OA (AOA) do not fully overlap. Key differences include changes in the subchondral bone and inflammatory signaling [2]. Other Questions in this consensus go into detail on this topic. The lack of FDA-approved DMOADs raises concerns about the reliability of the young PTOA animal model in predicting responses in human clinical trials. This review aimed to determine whether testing DMOADs in both PTOA and AOA is necessary.

PubMed and Scopus were searched for potentially eligible studies from data inception to January 2026. The search strategy included terms such as “animal osteoarthritis models,” “surgically induced osteoarthritis,” “age-related osteoarthritis,” and “disease-modifying osteoarthritis drugs (DMOADs)”. In our initial literature review, 691 records were retrieved, and two researchers independently screened the titles and abstracts of all 691 studies. 547 studies were then subjected to full-text review. Ultimately, a total of 48 studies were included in the review. After full-text screening, studies that lacked a valid comparison, either due to discrepant dosages or the absence of an intervention in one model, were excluded. Ultimately, a total of 48 were included in the review. The major findings from the same study or across studies are summarized in **Tables 1** & **2**, respectively.

Table 1. PTOA vs. AOA comparison in the same article.

Article	DMOADs	Animal species	Sex	PTOA Induction Method	Age of old animals	Conclusion from two models
[3]	Blockade of Sirt1 cleavage	C57BL/6J WT mice	F	DMM	17 months	Overall consistent
[4]	AAV5–kindlin-2	mice	N/A	DMM	24 months	Consistent

[5]	ESC-sEVs	C57BL/6J mice	M	ACLT	24 months	Consistent
[6]	Exofenadine and AACOCF3	C57BL/6J mice	N/A	DMM	24 months	Consistent
[7]	NE52-QQ57	C57BL/6J mice	M	DMM	24 months	Consistent
[8]	Nicotinamide riboside	C57BL/6J mice	M	MCL-MM	14 months	Consistent
[9]	LNP-FGF18 mRNA	C57BL/6J mice	N/A	DMM	24 months	Consistent
[10]	PGDHi	C57BL/6J mice	N/A	Tibia loading	24 to 28 months	Consistent

ACLT, Anterior Cruciate Ligament Transection; DMM, Destabilization of the Medial Meniscus; PTOA, Posttraumatic Osteoarthritis; MCL-MM, medial collateral ligament-medial meniscus; AOA, Age-Associated Osteoarthritis.

Table 2. PTOA vs. AOA comparison in different articles.

DMOADs	PTOA reference	Animal species	Sex	PTOA Induction Method	AOA reference	Animal species	Sex	Age of old animals	Conclusion from two OA models
Chondroitin sulfate	[11]	NZW Rabbits	M	ACLT + PMMT	[12]	Guinea pigs	F	18 months	Consistent
	[13]	NZW Rabbits	F	CCLT					
Metformin	[14]	SD rats	N/A	DMM	[15]	C57BL /6J mice	M	17 months	Consistent
Glucosamine	[16]	C57BL/6J mice		DMM	[12]	Guinea pigs	F	18 months	Consistent
	[17]	NZW Rabbits	M	ACLT					
	[18]	C57/BL6 mice	M	DMM					
	[18]	New NZW Rabbits	F	ACLT					
	[11]	NZW Rabbits	M	ACLT + PMMT					
	[13]	NZW Rabbits	F	CCLT					
	[19]	SD rats	M	ACLT					
	[20]	Rat	N/A	KTI					
Rapamycin	[21]	C57BL/6 mice		DMM	[22]	Guinea pig	M	8 months	Inconsistent
	[23]	C57Bl/6 mice		DMM					
	[24]	Db/db mice	M	MMTL + MCL					

Pharmacologic iron chelator DFO	25	C57/B6 mice	N/A	MMTL + MCL	26	Guinea pigs	N/A	30 weeks	Consistent
Bisphosphonate	27	Beagles	N/A	ACLT	28	Guinea pigs	M	9 months	Inconsistency
	29	C57BL/6 & FVB/NJ mice	M	Compressive loading					
	23	C57BL/6 mice	N/A	Mechanical loading					
	30	SD rats	N/A	MMx					
MSCs	31	SD rats		ACLT	32	Guinea pigs	M	10 months	Inconsistent
	33	Ripollesa-Lacona breed	F	Condylar and meniscal injuries					
	34	mature Japanese white rabbits	N/A	ACLT					
	35	NZW Rabbits	M	Osteochondral defect					
	36	NZW Rabbits	N/A	ACLT					
	37	Minipigs	F	Trochlear groove full-thickness cartilage injury					
	38	Wistar rat	N/A	ACLT					
	39	Horse	N/A	Osteochondral fragment					
Doxycycline	40	C57BL/6 mice	M	ACLR	41	Guinea pigs	N/A	9-11 months	Overall consistent
	42	SD rats	N/A	ACLR					
Icariin	43	SD Rats	N/A	Full-thickness cartilage defect + early treadmill exercise	44	Rabbit	N/A	D-galactose	Consistent
FGF18	45	BALB/c mice	N/A	ACLT	9	C57BL/6J mice	N/A	24 months	Consistent
	46	ICR mice	F	ACLT					
	47	SD rats	M	DMM					
	48	SD rats	F	TMJ partial discectomy					
	49	SD rats	M	Meniscal tear procedure					

[28]	C57BL/6 mice	M	DMM	

NZW Rabbits, New Zealand white rabbits; MMx, Medial Meniscectomy Surgery; KTI, Knee Triad Injury surgery

Most of the potential DMOADs, including metformin [14], glucosamine [11,18,20,50-53], chondroitin sulfate [11,52], rapamycin [24,54,55], fibroblast growth factor 18 [9,28,45-49], small-molecule inhibitor of 15-hydroxy prostaglandin dehydrogenase [10], and mesenchymal stem cells (MSCs) [31,34,36,38,39,56-58], have been primarily evaluated in PTOA models. It was found that sometimes the same therapeutic agents show inconsistent efficacy when tested in AOA models—an observation exemplified by the conflicting results for rapamycin [22,24,54,55], bisphosphonates [23,27,29,30,59], and MSCs [31,32,34,36,38,39,56-58] tested in PTOA and AOA models.

Given that not all listed DMOADs have been tested in PTOA and AOA using the same species, we had to evaluate results from studies using different species. Specifically, rapamycin [24,54,55] and bisphosphonate [23] were shown to alleviate osteoarthritis in PTOA mice, as evidenced by reduced histological scores. Since we could not find relevant studies testing them on AOA mice, we compared these findings to a study using Dunkin-Hartley (DH) guinea pigs, which naturally develop progressive osteoarthritis. Interestingly, bisphosphonate demonstrated no disease-modifying effects in the DH guinea pigs [59], and rapamycin-induced hyperglycemia is associated with exacerbated AOA [22]. Given the inconsistent conclusions from different animal models, it remains unclear which animal species are best for predicting drug efficacy in humans.

It should be noted that even if the same therapeutic effects were observed, the extent of response to the treatments may differ. For example, in the aging OA model, SW033291 reduced the Sumit OARSI score of aged mice from ~25 to <10 [10]. In contrast, the OARSI score decreased from ~25 to ~15 after SW03329 treatment.

In summary, while PTOA models are invaluable for testing therapies, researchers can determine whether a therapeutic candidate has the biological "stamina" to function in an aged human joint by integrating aging models into the preclinical workflow. This dual-model validation is particularly imperative for agents targeting conserved pathological pathways shared by traumatic and age-related OA, such as those modulating cellular senescence, chronic inflammation, and cartilage matrix homeostasis. Only through such cross-model validation can we account for model-specific variations in shared pathway activation and rigorously confirm the true efficacy and mechanistic consistency of DMOAD across distinct OA etiologies, a critical step to ensure preclinical findings are clinically translatable. In this process, the biological variables of the animals, in particular species and sex, need to be considered. Moreover, the molecular differences between PTOA and AOA have been documented. The presence of drug targets must be validated before testing DMOADs. Lastly, aging-associated OA can be spontaneous or induced by trauma. Research has shown that aged mice exhibit significantly greater cartilage degeneration and osteophyte formation compared to young mice following ACL rupture [60]. Whether testing DMOADs in aged animals with PTOA is necessary requires further investigation. It should be noted that the findings can be limited because we were unable to include unpublished negative results, meaning that tested DMOADs showed no therapeutic effect.

Reference

1. Collaborators, G.B.D.O. Global, regional, and national burden of osteoarthritis, 1990-2020 and projections to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet Rheumatol* **5**, e508-e522 (2023).
2. Iijima, H.*, et al.* Meta-analysis Integrated With Multi-omics Data Analysis to Elucidate Pathogenic Mechanisms of Age-Related Knee Osteoarthritis in Mice. *J Gerontol A Biol Sci Med Sci* **77**, 1321-1334 (2022).
3. Maatuf, Y.H.*, et al.* Diverse Response to Local Pharmacological Blockade of Sirt1 Cleavage in Age-Induced versus Trauma-Induced Osteoarthritis Female Mice. *Biomolecules* **14**(2024).
4. Wu, X.*, et al.* Kindlin-2 preserves integrity of the articular cartilage to protect against osteoarthritis. *Nat Aging* **2**, 332-347 (2022).
5. Feng, K.*, et al.* ESC-sEVs alleviate non-early-stage osteoarthritis progression by rejuvenating senescent chondrocytes via FOXO1A-autophagy axis but not inducing apoptosis. *Pharmacol Res* **209**, 107474 (2024).
6. Huang, G.*, et al.* Cytosolic phospholipase A2 as a therapeutic target for degenerative joint diseases. *Bone Res* **13**, 86 (2025).
7. Li, R.*, et al.* The proton-activated G protein-coupled receptor GPR4 regulates the development of osteoarthritis via modulating CXCL12/CXCR7 signaling. *Cell Death Dis* **13**, 152 (2022).
8. Wu, X.*, et al.* Altered nicotinamide adenine dinucleotide metabolism drives cartilage degeneration and osteoarthritis. *Clin Transl Med* **15**, e70513 (2025).
9. Kong, K.*, et al.* Delivery of FGF18 using mRNA-LNP protects the cartilage against degeneration via alleviating chondrocyte senescence. *J Nanobiotechnology* **23**, 34 (2025).
10. Singla, M.*, et al.* Inhibition of 15-hydroxy prostaglandin dehydrogenase promotes cartilage regeneration. *Science*, eadx6649 (2025).
11. Roman-Blas, J.A.*, et al.* The combined therapy with chondroitin sulfate plus glucosamine sulfate or chondroitin sulfate plus glucosamine hydrochloride does not improve joint damage in an experimental model of knee osteoarthritis in rabbits. *Eur J Pharmacol* **794**, 8-14 (2017).
12. Taniguchi, S.*, et al.* Long-term oral administration of glucosamine or chondroitin sulfate reduces destruction of cartilage and up-regulation of MMP-3 mRNA in a model of spontaneous osteoarthritis in Hartley guinea pigs. *J Orthop Res* **30**, 673-678 (2012).
13. Sifre, V.*, et al.* Improved Joint Health Following Oral Administration of Glycosaminoglycans with Native Type II Collagen in a Rabbit Model of Osteoarthritis. *Animals* **12**(2022).
14. Da, W.*, et al.* Metformin-Loaded Tannic Acid Nanoparticles Attenuate Osteoarthritis by Promoting Chondrocyte Mitochondria Homeostasis Based on Mitocytosis. *Biomacromolecules* **26**, 1507-1519 (2025).
15. Hou, J.*, et al.* Zwitterion-Lubricated Hydrogel Microspheres Encapsulated with Metformin Ameliorate Age-Associated Osteoarthritis. *Adv Sci (Weinh)* **11**, e2402477 (2024).
16. Kang, D.*, et al.* Regulation of senescence-associated secretory phenotypes in osteoarthritis by cytosolic UDP-GlcNAc retention and O-GlcNAcylation. *Nature Communications* **16**(2025).
17. Lu, H.T.*, et al.* Alterative effects of an oral alginate extract on experimental rabbit osteoarthritis. *Journal of Biomedical Science* **22**(2015).

18. Mével, E.*, et al.* Olive and grape seed extract prevents posttraumatic osteoarthritis damages and exhibits in vitro anti IL-1β activities before and after oral consumption. *Sci Rep* **6**, 33527 (2016).
19. Zhang, R.*, et al.* Therapeutic effect of Huzhangoside D in rats with knee osteoarthritis induced by anterior cruciate ligament transection. *Pharmacognosy Magazine* **17**, 112-119 (2021).
20. Panahifar, A.*, et al.* Development and reliability of a multi-modality scoring system for evaluation of disease progression in preclinical models of osteoarthritis: celecoxib may possess disease-modifying properties. *Osteoarthritis Cartilage* **22**, 1639-1650 (2014).
21. Dhanabalan, K.M.*, et al.* Intra-articular injection of rapamycin microparticles prevent senescence and effectively treat osteoarthritis. *Bioengineering and Translational Medicine* **8**(2023).
22. Minton, D.M., Elliehausen, C.J., Javors, M.A., Santangelo, K.S. & Konopka, A.R. Rapamycin-induced hyperglycemia is associated with exacerbated age-related osteoarthritis. *Arthritis Res Ther* **23**, 253 (2021).
23. Ziemian, S.N., Witkowski, A.M., Wright, T.M., Otero, M. & van der Meulen, M.C.H. Early inhibition of subchondral bone remodeling slows load-induced posttraumatic osteoarthritis development in mice. *J Bone Miner Res* **36**, 2027-2038 (2021).
24. Ribeiro, M.*, et al.* Diabetes-accelerated experimental osteoarthritis is prevented by autophagy activation. *Osteoarthritis Cartilage* **24**, 2116-2125 (2016).
25. Guo, Z.*, et al.* Deferoxamine alleviates chondrocyte senescence and osteoarthritis progression by maintaining iron homeostasis. *Int Immunopharmacol* **139**, 112619 (2024).
26. Burton, L.H.*, et al.* Systemic administration of a pharmacologic iron chelator reduces cartilage lesion development in the Dunkin-Hartley model of primary osteoarthritis. *Free Radic Biol Med* **179**, 47-58 (2022).
27. Xu, L.*, et al.* Early zoledronate treatment inhibits subchondral bone microstructural changes in skeletally-mature, ACL-transected canine knees. *Bone* **167**, 116638 (2023).
28. Huang, Z., Zhao, W., Lan, J., Lin, Y. & Gao, X. Fibroblast growth factor 18 stimulates chondrocyte proliferation by modulating FOXN2 to mitigate posttraumatic osteoarthritis in a mouse model. *Front Bioeng Biotechnol* **13**, 1615124 (2025).
29. Adebayo, O.O.*, et al.* Role of subchondral bone properties and changes in development of load-induced osteoarthritis in mice. *Osteoarthritis Cartilage* **25**, 2108-2118 (2017).
30. Panahifar, A., Maksymowych, W.P. & Doschak, M.R. Potential mechanism of alendronate inhibition of osteophyte formation in the rat model of posttraumatic osteoarthritis: evaluation of elemental strontium as a molecular tracer of bone formation. *Osteoarthritis Cartilage* **20**, 694-702 (2012).
31. Zhao, Z.*, et al.* Days 7 to 14 May Represent an Optimal Window for Stem Cell-Based Treatment in a Rat Model of Anterior Cruciate Ligament Transection-Induced Posttraumatic Osteoarthritis. *Am J Sports Med* **53**, 1629-1640 (2025).
32. Afzali, M.F.*, et al.* Intravenous injection of adipose-derived mesenchymal stromal cells benefits gait and inflammation in a spontaneous osteoarthritis model. *J Orthop Res* **41**, 902-912 (2023).
33. Caminal, M.*, et al.* Use of a chronic model of articular cartilage and meniscal injury for the assessment of long-term effects after autologous mesenchymal stromal cell treatment in sheep. *New Biotechnology* **31**, 492-498 (2014).

34. Mahmoud, E.E., Adachi, N., Mawas, A.S., Deie, M. & Ochi, M. Multiple intra-articular injections of allogeneic bone marrow-derived stem cells potentially improve knee lesions resulting from surgically induced osteoarthritis: an animal study. *Bone Joint J* **101-b**, 824-831 (2019).
35. Nunoda, D., Yamamoto, K., Katori, Y. & Watanabe, Y. Effects of hyaluronic acid on extracellular matrix degradation in a rabbit osteoarthritis model. *Journal of Tokyo Medical University* **63**, 212-220 (2005).
36. Toghraie, F.S.*, et al.* Treatment of osteoarthritis with infrapatellar fat pad derived mesenchymal stem cells in Rabbit. *Knee* **18**, 71-75 (2011).
37. Wu, K.C., Chang, Y.H., Liu, H.W. & Ding, D.C. Transplanting human umbilical cord mesenchymal stem cells and hyaluronate hydrogel repairs cartilage of osteoarthritis in the minipig model. *Tzu Chi Medical Journal* **31**, 11-19 (2018).
38. Ueki, H.*, et al.* Effect of transplanted mesenchymal stem cell number on the prevention of cartilage degeneration and pain reduction in a posttraumatic osteoarthritis rat model. *J Orthop Sci* **26**, 690-697 (2021).
39. Andersen, C.*, et al.* Integrin α10β1-Selected Mesenchymal Stem Cells Reduce Pain and Cartilage Degradation and Increase Immunomodulation in an Equine Osteoarthritis Model. *Cartilage* **16**, 250-264 (2025).
40. Zhang, X.*, et al.* Matrix Metalloproteinase Inhibition With Doxycycline Affects the Progression of Posttraumatic Osteoarthritis After Anterior Cruciate Ligament Rupture: Evaluation in a New Nonsurgical Murine ACL Rupture Model. *Am J Sports Med* **48**, 143-152 (2020).
41. Bowyer, J., Heapy, C.G., Flannelly, J.K., Waterton, J.C. & Maciewicz, R.A. Evaluation of a magnetic resonance biomarker of osteoarthritis disease progression: doxycycline slows tibial cartilage loss in the Dunkin Hartley guinea pig. *Int J Exp Pathol* **90**, 174-181 (2009).
42. Cao, M.*, et al.* Doxycycline Promotes Graft Healing and Attenuates Posttraumatic Osteoarthritis After Anterior Cruciate Ligament Reconstruction in a Rat Model. *Am J Sports Med* **51**, 461-475 (2023).
43. Xiang, W.*, et al.* Role of IFT88 in icariin-regulated maintenance of the chondrocyte phenotype. *Mol Med Rep* **17**, 4999-5006 (2018).
44. Zhang, W., Li, R., Wang, S., Mu, F. & Jia, P. Effect of Chinese traditional herb Epimedium grandiflorum C. Morren and its extract Icariin on osteoarthritis via suppressing NF-kappaB pathway. *Indian J Exp Biol* **51**, 313-321 (2013).
45. Tong, M.J.*, et al.* A Bionic Thermosensitive Sustainable Delivery System for Reversing the Progression of Osteoarthritis by Remodeling the Joint Homeostasis. *Adv Healthc Mater* **13**, e2303792 (2024).
46. Sun, M.*, et al.* Targeted Therapy of Osteoarthritis via Intra-Articular Delivery of Lipid-Nanoparticle-Encapsulated Recombinant Human FGF18 mRNA. *Adv Healthc Mater* **13**, e2400804 (2024).
47. Yao, X.*, et al.* Fibroblast growth factor 18 exerts anti-osteoarthritic effects through PI3K-AKT signaling and mitochondrial fusion and fission. *Pharmacol Res* **139**, 314-324 (2019).
48. Kuang, Y.*, et al.* Dual-functional ROS-responsive hydrogel alleviates temporomandibular joint osteoarthritis by enhancing cartilage repair and mitigating inflammation. *Mater Today Bio* **33**, 102103 (2025).

49. Moore, E.E.*, et al.* Fibroblast growth factor-18 stimulates chondrogenesis and cartilage repair in a rat model of injury-induced osteoarthritis. *Osteoarthritis Cartilage* **13**, 623-631 (2005).
50. Kang, D.*, et al.* Regulation of senescence-associated secretory phenotypes in osteoarthritis by cytosolic UDP-GlcNAc retention and O-GlcNAcylation. *Nat Commun* **16**, 1094 (2025).
51. Lu, H.T.*, et al.* Alterative effects of an oral alginate extract on experimental rabbit osteoarthritis. *J Biomed Sci* **22**, 64 (2015).
52. Sifre, V.*, et al.* Improved Joint Health Following Oral Administration of Glycosaminoglycans with Native Type II Collagen in a Rabbit Model of Osteoarthritis. *Animals (Basel)* **12**(2022).
53. Zhang, R.J.*, et al.* Therapeutic effect of Huzhangoside D in rats with knee osteoarthritis induced by anterior cruciate ligament transection. *Pharmacognosy Magazine* **17**(2021).
54. Dhanabalan, K.M.*, et al.* Intra-articular injection of rapamycin microparticles prevent senescence and effectively treat osteoarthritis. *Bioeng Transl Med* **8**, e10298 (2023).
55. Caramés, B.*, et al.* Autophagy activation by rapamycin reduces severity of experimental osteoarthritis. *Ann Rheum Dis* **71**, 575-581 (2012).
56. Caminal, M.*, et al.* Use of a chronic model of articular cartilage and meniscal injury for the assessment of long-term effects after autologous mesenchymal stromal cell treatment in sheep. *N Biotechnol* **31**, 492-498 (2014).
57. Nunoda, D. Effects of hyaluronic acid on extracellular matrix degradation in a rabbit osteoarthritis model. *The Journal of Tokyo Medical University* **63**, 212-220 (2005).
58. Wu, K.C., Chang, Y.H., Liu, H.W. & Ding, D.C. Transplanting human umbilical cord mesenchymal stem cells and hyaluronate hydrogel repairs cartilage of osteoarthritis in the minipig model. *Tzu Chi Med J* **31**, 11-19 (2019).
59. Thomsen, J.S., Straarup, T.S., Danielsen, C.C., Oxlund, H. & Brüel, A. No effect of risedronate on articular cartilage damage in the Dunkin Hartley guinea pig model of osteoarthritis. *Scand J Rheumatol* **42**, 408-416 (2013).
60. Sebastian, A.*, et al.* Global Gene Expression Analysis Identifies Age-Related Differences in Knee Joint Transcriptome during the Development of Posttraumatic Osteoarthritis in Mice. *Int J Mol Sci* **21**(2020).